



Research Highlight

# Exercise, the endocannabinoid system and metabolic health

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## 1. The endocannabinoid system in obesity and metabolic disorders

As obesity and associated metabolic disorders, such as type 2 diabetes and dyslipidemia, are becoming one of the most serious health problems worldwide, development of effective therapies is a high priority. In the search for treatments, the recently discovered endocannabinoid system (ECS) has begun to garner attention, and a wealth of research is now focusing on this unique neuromodulatory system named after the plant that led to its discovery.<sup>1</sup>

The ECS consists of G protein-coupled cannabinoid receptors (CB1 and CB2), their endogenous lipid-derived ligands (endocannabinoids, N-arachidonylethanolamine, named anandamide (AEA) and 2-arachidonoylglycerol (2-AG)) and the enzymes for ligand synthesis and degradation. Endocannabinoids, the organic derivative of cannabis, produced naturally in the body, are well known to modulate many cognitive and emotional processes, through which they influence multiple behavioral responses.<sup>2</sup> However, a number of studies published in recent years indicate that endocannabinoids are also key modulators of energy balance through central and peripheral mechanisms.<sup>1</sup> In the central nervous system, the activation of CB1 receptors by endocannabinoids increases food intake, whereas in the peripheral organs, such as gastrointestinal tract, liver, adipose tissue, and skeletal muscle, endocannabinoids are involved in the regulation of nutrient absorption and glucose and lipid metabolism.<sup>3</sup> Considering the important

regulatory role of the ECS in energy metabolism, it is not surprising to observe its dysregulation in obesity.

Recent data suggest that ECS overactivity is associated with increased lipogenesis, insulin resistance, and dyslipidemia.<sup>4</sup> Hence, the ECS has become a promising pharmacological target in combating obesity and the associated metabolic disorders.<sup>5</sup> Although some clinical trials with specific CB1 receptor antagonists/inverse agonists have been successful in terms of reduction of body weight and amelioration of obesity-related metabolic abnormalities, the adverse central and peripheral side effects of these compounds have seriously limited their therapeutic potential.<sup>6</sup> However, recent findings show that combined calorie restriction and aerobic exercise can modulate endocannabinoid-related gene expression in adipose tissue of obese women during weight loss, suggesting that ECS may link exercise with metabolic adaptations and energy regulation.<sup>7</sup>

## 2. Plausible metabolic implications of exercise-induced ECS activation

Apart from the above cited study, the metabolic effects of ECS following exercise in humans have not been studied. Several lines of evidence indicate that the ECS may participate in the adaptive responses to exercise. A recent review by Heyman et al.<sup>8</sup> provides a comprehensive summary of the topic, and several possible mechanisms can be suggested. First, plasma AEA increases significantly following acute strenuous aerobic exercise in humans, while circulating levels of 2-AG appear not to be influenced by exercise.<sup>9–10</sup> Since AEA has vasodilatory<sup>11</sup> and bronchodilatory<sup>12</sup> effects, increase in circulating AEA may aid exercise performance by facilitating blood flow and breathing during exercise. AEA has also been shown to improve insulin sensitivity, glucose uptake and mitochondrial biogenesis in human skeletal muscle cells,<sup>13</sup> and inhibit fatty acid and cholesterol synthesis in hepatocytes.<sup>14</sup> These findings indicate that while CB1

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signaling negatively modulates insulin signaling and substrate oxidation in metabolically active tissues,<sup>15</sup> AEA has opposite effects, which appear to be mediated independently of the cannabinoid receptors.

Second, exercise-induced elevation of plasma AEA is intensity-dependent. According to a recent study, only moderate exercise intensities (~70%–85% age-adjusted maximum heart rate) significantly increase circulating levels of AEA.<sup>16</sup> This observation is consistent with findings that several cardio-metabolic risk factors are also most favorably affected by moderate-intensity exercise compared to low-intensity exercise.<sup>17</sup>

Third, chronic aerobic exercise has been shown to attenuate CB1 mRNA over-expression in visceral and subcutaneous adipose tissues of obese rats fed with a high-fat diet.<sup>18</sup> Our unpublished data corroborate these findings by showing that chronic aerobic exercise decreases CB1 protein expression in skeletal muscle of mice fed with a high fat diet. Given the crucial role of skeletal muscle in whole body energy expenditure and substrate oxidation, especially during exercise, this observation may turn out to be of great importance for the treatment of obesity and the associated metabolic disorders.

Finally, it has been demonstrated that glucocorticoids increase AEA in limbic structures,<sup>19</sup> indicating that endocannabinoid signaling is evoked by stress-induced activation of the hypothalamic-pituitary-adrenal axis,<sup>20</sup> which in turn, is inhibited by endocannabinoid signaling via non-genomic fast-feed mechanism.<sup>21</sup> The concurrent increase in AEA and cortisol observed during intense exercise<sup>10</sup> suggests that the increase in plasma AEA during exercise may be ascribed to the exercise-induced alterations in circulating cortisol. Thus, it seems that the ECS activation may be essential for the recovery from a transient stressful condition, such as intense physical exercise.

### 3. Future challenges

Accumulating evidence shows that the ECS is associated with physical activity, obesity and related metabolic disorders. However, to date, no data on the responses of the ECS to exercise in patients with metabolic diseases have been published. Whether acute or chronic exercise can attenuate ECS over-activity in humans remains to be confirmed. Both mechanistic and randomized controlled studies are needed to confirm whether the ECS is involved in the beneficial effects of exercise on metabolism and energy balance. Understanding the connection between exercise, ECS and metabolism deserves further investigation as exercise may represent a complementary approach to modulate ECS and treat and prevent obesity and metabolic disorders.

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